Towards a new WHO classification of renal cell tumor: what the clinician needs to know-a narrative review

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Review Article on Update on Molecular Classification and Individualized Treatments of Genitourinary Tumors

Towards a new WHO classification of renal cell tumor: what the clinician needs to know—a narrative review

Alessia Cimadamore[1], Liang Cheng[2], Marina Scarpelli[1], Francesco Massari[3], Veronica Mollica[3], Matteo Santoni[4], Antonio Lopez-Beltran[5], Rodolfo Montironi[1], Holger Moch[6]

[1]Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy; [2]Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Division of Oncology, S. Orsola-Malpighi Hospital, Bologna, Italy; [4]Oncology Unit, Macerata Hospital, 62012 Macerata, Italy; [5]Department of Surgery, Cordoba University Medical School, Cordoba, Spain; [6]Department of Pathology and Molecular Pathology, University and University Hospital Zurich, CH-8091 Zurich, Switzerland

Contributions: (I) Conception and design: A Cimadamore, R Montironi, H Moch; (II) Administrative support: R Montironi; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: A Cimadamore, F Massari, V Mollica, M Santoni; (V) Data analysis and interpretation: A Lopez-Beltran, L Cheng, M Scarpelli; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alessia Cimadamore. Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Via Conca 71, I–60126 Ancona, Italy. Email: alessiacimadamore@gmail.com.

Abstract: In 1952, renal cell carcinomas had been divided into 2 categories—clear cell or granular cell—depending upon their cytoplasmic staining characteristics. In the following years, the inventory of renal epithelial tumors has expanded by the addition of tumors named by their architectural pattern (i.e., papillary RCC, tubulocystic RCC), anatomic location (i.e., collecting duct carcinoma, renal medullary carcinoma), associated diseases (i.e., acquired cystic disease-associated RCCs). With the extensive application of molecular diagnostic techniques, it becomes possible to detect genetic distinctions between various types of renal neoplasm and discover new entities, otherwise misdiagnosed or diagnosed as unclassified RCC. Some tumors such as ALK rearrangement-associated RCC, MiT family translocation renal carcinomas, SDH-deficient renal cancer or FH-deficient RCC, are defined by their molecular characteristics. The most recent World Health Organization (WHO) classification of renal neoplasms account for more than 50 entities and provisional entities. New entities might be included in the upcoming WHO classification. The aim of this review is to summarise and discuss the newly acquired data and evidence on the clinical, pathological, molecular features and on the prognosis of new RCC entities, which will hopefully increase the awareness and the acceptance of these entities among clinicians and improve prognostication for individual patients.

Keywords: Renal cell carcinoma; classification; molecular pathology; clear cell RCC; non-clear cells RCC; emerging entities; Von Hippel-Lindau gene (VHL); fumarate hydratase (FH); succinate dehydrogenase (SDH); anaplastic lymphoma kinase (ALK)

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Introduction

In the last 70 years, from 1952 to 2020, the clinical spectrum of renal cell carcinomas (RCC) has expanded by the increased recognition of new entities and the refinements of existing categories (1,2). The classification system has grown along with electron microscopy, immunohistochemistry, cytogenetics, and molecular diagnostic techniques. Some tumors such as ALK rearrangement-associated RCC, MiT family translocation renal carcinomas, SDH-deficient renal cancer or FH-deficient RCC, are defined by their molecular characteristics (3). The most recent World Health Organization (WHO) classification of renal neoplasms

account for more than 50 entities and provisional entities (4,5). New entities might be included in the upcoming WHO classification.

However, besides an increasing understanding of the tumor histologies and biological behaviour, only few tumor entities have a specific treatment and ongoing clinical trial are still adopting the old classification of clear cells RCC (ccRCC) and non-clear cells RCC (nccRCC) as selection criteria (6).

This review will summarise and discuss the newly acquired data and evidence on the clinical, pathological, molecular features of the new entities included in the WHO 2016 classification and of the emerging/provision entities, which will hopefully increase the awareness and their acceptance among clinicians and improve prognostication for individual patients. A PubMed search using the keywords "renal cell carcinoma", "emerging entities", "provisional entities", "molecular classification", from 2005 and June 2020 was performed.

It is beyond the scope of this review to describe in detail the various diagnostic pathological features and immunohistochemical antibody expression of these tumors. Detailed information about each entities are available in all the cited papers. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1150).

Narrative review

New renal tumor entities

Newly recognized epithelial renal tumours in the 2016 WHO classification are HLRCC associated RCC, SDH-deficient RCC, tubulocystic RCC, acquired cystic RCC, and clear cell papillary RCC (4).

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome-associated renal cell carcinoma/ FH-deficient RCC

HLRCC associated RCC are highly aggressive tumors that early metastasize, with frequent spread to regional lymph nodes, even if of small size (7,8). These rare tumors occur in people affected by an autosomal dominant tumor syndrome associated with germline mutations in the fumarate hydratase (FH) gene at chromosome 1q42. Patients with HLRCC syndrome usually present cutaneous leiomyomas and in female uterine leiomyoma and less frequently leiomyosarcomas (9,10). Thirty percent of the patients can also develop RCC, characterized by type 2 papillary growth pattern and large nucleus with prominent orangiophilic or eosinophilic nucleolus, surrounded by a clear halo, resembling a viral inclusion which is the hallmark of these neoplasms. Same cytological features have been also described in uterine leiomyoma of these syndromic patients (11). An accurate diagnosis of these tumors is of primary importance for the correct management of the patients and their families. The germline mutations of the FH gene is the specific genetic alteration for these tumors and is detectable by IHC for FH antibody (loss of expression) or for S-2(2-succino)-cysteine (2SC) (strong and diffuse nuclear and cytoplasmic stain) or by molecular testing (12). In the setting of uncertain clinical and family history and unknown genetic status, is recommended to use "FH-deficient RCC" for tumors that show IHC-negative staining for FH and strong 2SC reactivity (12) (*Figure 1A* and *1B*). Report of two syndromic cases treated in first-line with bevacizumab/erlotinib showed significant and long lasting response (13).

Succinate dehydrogenase deficient neoplasia

These category of tumors account for about 0.05% to 0.2% of renal neoplasms and are defined by the double-hit inactivation of one of the SDH genes (SDHA, SDHB, SDHC, SDHD, and SDHAF2), an event that occurs only rarely in the absence of a germline mutation (14,15). Patients with germline mutation can also develop pheochromocytomas/paragangliomas, gastrointestinal stromal tumors, and pituitary adenomas. Presence of these rare type of tumors in the same patient/family should raise the suspicion of a germline mutation and encourage genetic counselling. The majority of the cases have loss of SDHB gene identifiable by loss of immunohistochemical stain. The median age at presentation is around 40 years with a wide range (14–76 years), they are typically solitary masses, multifocal and bilateral in 30% of patients. Low grade SDH-deficient RCC and without coagulative necrosis are associated with good outcome, while presence of necrosis, high grade and sarcomatoid features can present metastatic spread in 70% of the cases (16-18) (*Figure 1C*).

Tubulocystic RCC

Tubulocystic renal cell carcinoma (TCC RCC) was first comprehensively described by George Farrow and then by Amin *et al.* under the spectrum of collecting duct carcinoma. Because these tumors were entirely composed of tubules and

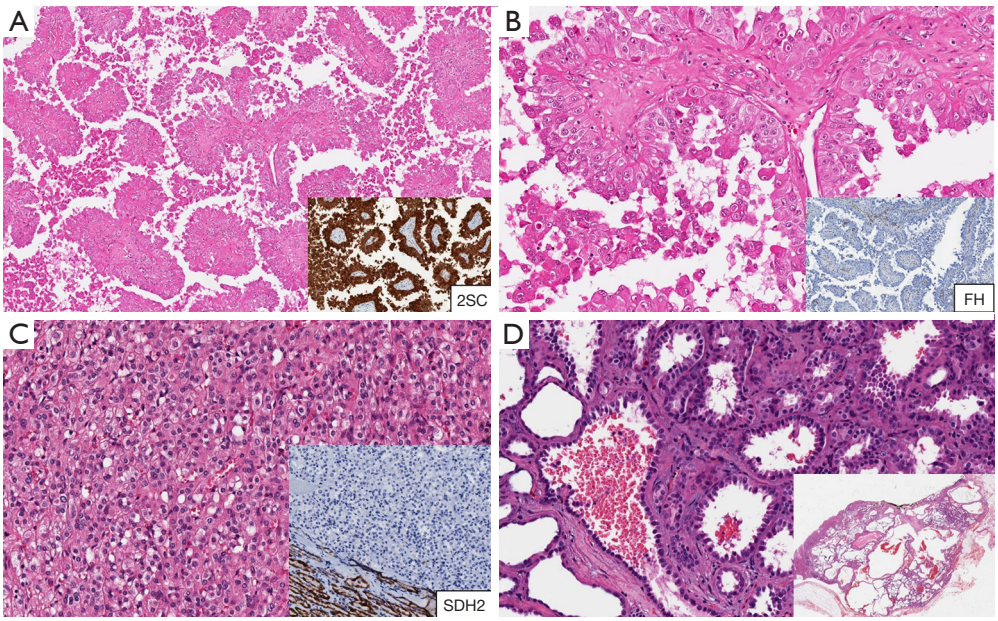

Figure 1 FH-Deficient RCC, at low (2×) (A) and high magnification (20×) (B), with strong and diffuse positivity for 2SC and loss of FH expression (inserts); Succinate Dehydrogenase Deficient Neoplasia (10×) (C) with loss of SDH2 expression (insert); Tubulo-cystic RCC (10×) (D), at low magnification (insert).

duct-like structures, it was initially call low-grade collecting duct carcinoma for its appearance and its significantly different behavior compared to the classical highly aggressive collecting duct carcinomas. Genetic alteration of TCC RCC are distinct from those of ccRCC, pRCC, ChRCC and also from collecting duct carcinomas. More than 80 cases have been reported so far with strong prevalence in males (male/female ratio of 7:1) and higher incidence in the fifth and sixth decade. Most of the tumors are cystic and in pT1 stage and behave in an indolent fashion. Only rare cases presented metastasis to the pelvic lymph nodes, bone, liver and peritoneum (19-23) (*Figure 1D*).

Clear cell papillary RCC

Clear cell Papillary RCC (CCPRCC) is thought to have a prevalence rate of approximately 1–4% and that about 6% of low-grade ccRCC are, in fact, CCPRCC, making this entity the fourth most common RCC subtype. The characteristic immunoprofile with diffuse cytokeratin 7 staining, GATA3 positivity, "cup-shaped" carbonic anhydrase IX staining distribution, and negative results for AMACR and CD10, along with the absence of VHL alterations in almost all tumor, distinguish this entity from ccRCC and papillary RCC. When the immunohistochemistry shows an imperfect staining pattern, current recommendations advise to classify such tumors as ccRCC and to refers to genetic analysis for VHL mutation or chromosome 3p loss (24-26) (*Figure 2A*,*B*,*C*).

Acquired cystic disease-associated renal cell carcinoma (ACD-RCC)

Patients with acquired cystic disease (ACD) of the kidney have a risk of develop a renal tumors about 100 times higher than the general population, a risk that increases with the duration of the dialysis. ACD-RCC is specific for the cystic disease condition and occurs only in end-stage renal disease patients, but patients with ACD can develop also other RCC histotypes. The vast majority of ACD-RCC present intratumoral calcium oxalate deposition in the luminal structures and in the stroma. These tumors have been usually detected at an early stage, thus the clinical course is usually indolent. Few cases with sarcomatoid component have been reported and were associated with poor outcome (27-30) (*Figure 2D*).

Emerging or provisional renal tumour entities

The 2016 WHO classification includes some rare entities, not yet well characterized in terms of morphology, immunohistochemical stain and genetic features, therefore

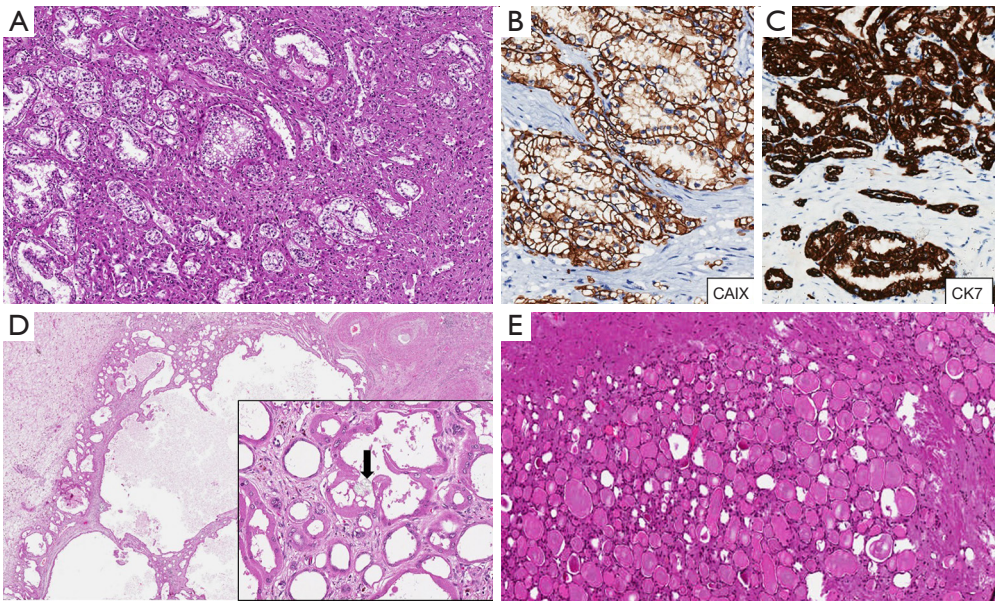

Figure 2 Clear cell papillary RCC. Clear cells of low nuclear grade, variable papillary, tubular-acinar and cystic architecture in a fibroleiomyomatous stroma (10×) (A), "cup-shaped" carbonic anhydrase IX staining distribution (20×) (B), strong and diffuse CK7 positivity (20×) (C). Acquired cystic disease-associated renal cell carcinoma (4×) (D), note the oxalate crystals (arrow) at higher magnification (insert); Thyroid like follicular RCC (4×) (E).

placed under the category "emerging/provisional tumors". These entities are thyroid-like follicular RCC, RCCs associated with ALK gene rearrangement, Renal cell carcinoma with (angio) leiomyomatous stroma and TCEB1 mutated RCC. RCC in neuroblastoma survivors was removed from 2016 WHO classification and its now considered an emerging entity.

Thyroid like follicular RCC

To data, less than 40 cases of Thyroid like follicular RCC have been reported, 27 in female and 12 in male patients and a median age of 35 years. These curious entities are characterized by structures resembling thyroid follicles with accumulation of inspissated colloid-like material that closely mimic a well-differentiated thyroid follicular neoplasms. The main differential diagnosis are a chronic pyelonephritis or a metastatic thyroid carcinoma. Thyroid like follicular RCC are in most of the cases indolent neoplasms. Few cases reported spread in hilar lymph nodes and distant metastasis, but all the patients survived after surgical resection (31-34) (*Figure 2E*).

Anaplastic lymphoma kinase (ALK) Rearrangement-Associated RCC (ALK-RCC)

ALK-RCC has been described in 2011 and less than 30 cases have been reported so far (35-43).

They are usually solitary tumor, not associated with any syndrome, with a slight prevalence in males and reported in a wide age range, including adolescents. Thirty% of the cases demonstrated malignant behavior with metastasis and death. Variable and multiple morphologies can be seen in this type of tumor and the definitive diagnosis can only be done by performing IHC for ALK antibody and FISH analysis for ALK rearrangement (44) (*Figure 3A,B*). Multiple ALK fusion gene partners have been identified. Mucinous background, intracytoplasmic mucin and myxoid changes have been reported in a subsets of cases and can be a helpful clue to recognize these rare tumor eligible for a potential targetable therapy. "ALK IHC screening for unclassifiable RCCs with heterogeneous features" has been proposed by Kuroda and colleagues (43).

Target therapy against ALK activation (i.e., ALK inhibitors alectinib and crizotinib) have been developed for ALK rearranged tumors and have proven efficacy and tolerability. Short term clinical and radiographic response to alectinib has been recently reported in 3 patients with metastatic EML4-ALK rearranged tumors (45). In children and adolescents ALK-RCC resembles renal medullary carcinoma and collecting duct carcinoma, are frequently

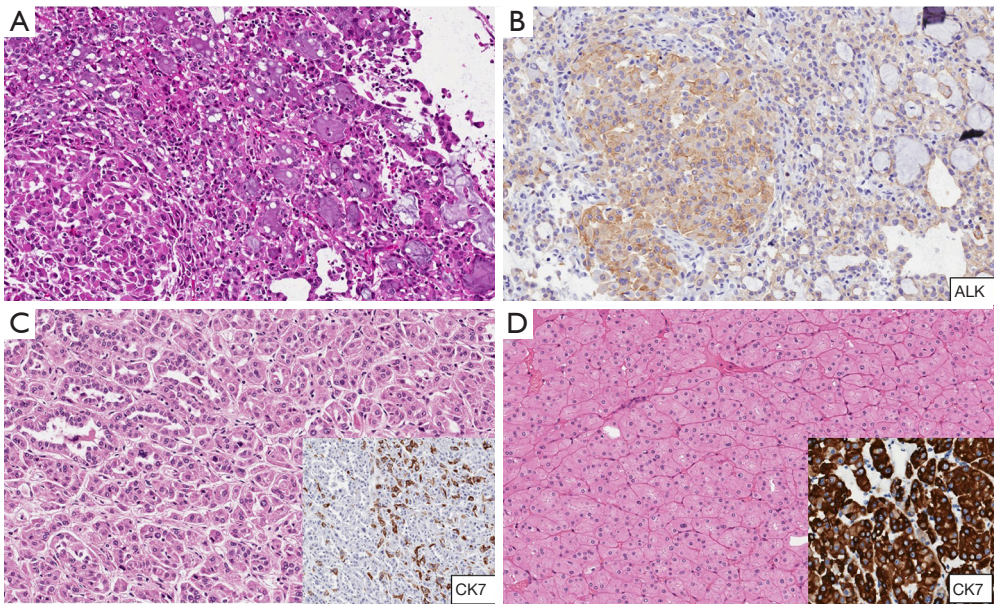

Figure 3 ALK Rearrangement-associated RCC (A, 10×) with mucinous background, ALK-IHC membrane expression (B, 10×); HOT (C, 10×) and LOT (D, 10×), with scant and diffuse CK7 expression, respectively (inserts, 20×).

located in the medulla or renal pelvis and harbor VCL-ALK and TPM3-ALK fusion. Until recently, VCL-ALK rearrangements has been reported only in pediatric patients of African American origin with the sickle-cell trait. Some cases in adult patients have been described as metanephric adenoma, mucinous tubular and spindle cell carcinoma, MiTF RCC (due to the positivity for TFE3 by IHC without FISH confirmed rearrangement for Xp11.2 translocation) (46,47).

The differential diagnosis in these cases is of great importance due to the differences in prognosis compared to a benign and indolent entities and to the implication in therapeutic choice for ALK rearranged tumors.

Renal cell carcinoma with (angio) leiomyomatous stroma (RCCLMS)

Multiple names have been used to describe this rare entity: mixed renal tumour with carcinomatous and fibroleiomyomatous components, RCC associated with prominent angioleiomyoma-like proliferation, clear cell RCC with smooth muscle stroma, RCC with clear cells, smooth muscle stroma and negativity for 3p deletion, RCC with leiomyomatous stroma, and RCC with angioleiomyomatous-like stroma. These rare tumors are constituted by two admixed components, epithelial—usually nest/tubules/papillary structure of clear cell, with low grade nuclei—and stromal—non-neoplastic leiomyomatous or fibroleiomyomatous (48-52).

The presence of a prominent leiomyomatous stroma is not a feature of a specific entity, but can be seen in otherwise typical ccRCC and even in papillary RCC.

According to recent publication by Shah and colleagues, the morphology, immunohistochemical features, and molecular alterations of RCCLMS distinguish this entity from CCRCC and CCPRCC. Of the 18 sporadic RCCLMS they included in their analysis, 4 harbour TSC1, 4 TSC2, 6 MTOR, and/or 2 TCEB1 mutations and all have an intact VHL gene. Their findings support the suggestion that these tumors represent the sporadic counterpart to morphologically identical tumors occurring in TSC patients (53).

TCEB1 Renal cell carcinoma

A small fraction of wt-VHL RCC are characterized by inactivation of the TCEB1 gene that encodes for a protein part of the E3 ubiquitin ligase complex. Inactivation of TCEB1 increases HIF stabilisation via the same mechanism as VHL inactivation. These tumors are often accompanied by loss of chromosome 8 (often in the form of monosomy). These new entity resembles ccRCC, express CAIX as well, and usually present thick fibromuscular bands transecting the tumor and clear cell cytology with voluminous

cytoplasm. Although initial data on this subset suggested that they are nonaggressive, recent reports of aggressive behaviour have been published (53-56).

New aspects in classic tumor entities

Clear cell RCC: VHL alterated and VHL wild type entities

Clear cell RCC is the most prevalent histotype among RCC, accounting for about 70% of all cases, historically defined by clear cell cytoplasm and a characteristic network of small, thin walled, vasculature. The majority of ccRCC are characterized by the biallelic loss of the VHL tumor suppressor gene in the short arm of chromosome 3 that can occurs via mutations, copy deletion and promoter hypermethylation. Patients affected by von Hippel–Lindau syndrome inherited a single inactivated copy of the VHL gene and usually develop other tumor types such as hemangioblastomas, pheochromocytoma, pancreatic cysts, endolymphatic sac tumor, and cystadenomas of the epididymis (men) or broad ligament of the uterus (women) (57-59). In the last decades, some tumor entities have been described with clear cell cytoplasm and showing morphological overlap with clear cell papillary RCC, RCC with (angio) leiomyomatous stroma, translocation carcinomas, and TCEB1 renal cancer. However, these tumors do not share the same genetic aberrations of ccRCC and should be distinguished from the classical VHL-mutated ccRCC (56). A correct classification of these tumors is relevant from a clinical prognostic point of view since these tumors (i.e., CCPRCC, RCCLMS, MiT family translocation RCC) are mostly indolent while others such as ccRCC VHL-wild type have been associated with a higher aggressiveness, sarcomatoid features and rapid progression (60-62).

Papillary renal cell carcinoma: more than just type 1 and type 2

Papillary RCC has seen the most marked changes during the last decade. It is a heterogeneous category that comprehends indolent entities and aggressive high lethal tumors. The molecular characterization published in 2016 distinguished two categories: type 1, the most uniform subgroup, typically associated with MET alterations, and type 2 tumors characterized by different genetic alterations (such as CDKN2A silencing, SETD2 mutations, TFE3 fusions, and increased expression of the NRF2-antioxidant response element pathway) and composed by multiple specific neoplasms rather than a single specific entity. A CpG island methylator phenotype (CIMP) has been reported in a FH deficient pRCC (often associated with the hereditary leiomyomatosis and renal cell carcinoma syndrome [HLRCC]) (63). Type 2 papillary RCC had worse outcomes compared to type 1, and usually have higher nuclear grade, higher stage and tumor size with a 6% of lymph nodes metastasis (64).

Chromophobe RCC: How to distinguish the good one from the bad one

Chromophobe RCC (ChRCC) accounts for approximately 5-7% of all adult renal tumors and it is usually composed of epithelial cells, polygonal pale cells, and eosinophilic cells, with accentuated cellular membranes, raisin-like nuclei and perinuclear halos. Due to constitutive atypia of the nuclei, the presence of binucleation, and the nucleolar prominence, the World Health Organization/International Society of Urologic Pathologists (WHO/ISUP) nucleolar system cannot be applied in ChRCC (4). However, a histological grading system with a prognostic validation is greatly needed. Its course is generally indolent but a minority of cases develop metastases and respond poorly to the currently available therapy. Grading system proposal are based on the presence of three parameters: sarcomatoid differentiation, histological coagulative tumor necrosis, and presence of mitosis (65-68).

Using such a grading system, a statistically significant difference was reported in overall survival in univariate analysis. However, low to medium concordance was reported in the identification of mitosis. Therefore, a two-tiered tumor grading system based only on presence of sarcomatoid differentiation and necrosis was proposed by Ohashi *et al.* This system showed high accuracy in prediction of time to progression, overall survival and high interobserver reproducibility (67,68).

From a molecular prospective, ChRCC is characterized by multiple chromosome losses (chromosome Y, 1,2,6,10,13,17.21), a reduced expression of "Copy-number alterations Yielding Cancer Liabilities Owing to Partial losS" (CYCLOPS) genes and TP53 and PTEN mutations (69). Patients with metastatic disease has an increased tumor mutation rates in these two genes and an imbalanced chromosome duplication (70). In difficult cases, chromosomal copy number alterations can be used for the differential diagnosis between the eosinophilic variant of

ChRCC and oncocytoma. Losses of chromosome 1 and Y has been found also in benign oncocytoma while losses of chromosomes 2, 6, 10, or 17 are not and can be used to exclude the benign entity (71-74). Recently the group of Ohashi *et al.* discovered that a reduced CDKN1A mRNA expression levels and CDKN1A immuno-negativity were associated with poor outcome in ChRCC (75).

In case of hybrid tumors and in patients with multiple oncocytic tumors, the analysis of FLCN gene (folliculin) can be performed to support the diagnosis of Birt-Hogg-Dubè syndrome (44).

High-grade oncocytic tumor (HOT) and Low-grade oncocytic tumor (LOT)

In the spectrum of oncocytic tumors difficult to classify, two distinct entities have been recently proposed: High-grade oncocytic tumor (HOT) and Low-grade oncocytic tumor (LOT). HOT and LOT are eosinophilic tumors that do not fit in any of the currently recognized tumor categories, in particular oncocytic tumors such as oncocytoma, ChRCC, hybrid oncocytic tumors either sporadic or syndromic. Twenty-two HOT cases have been published since now, one sporadic and just one in a patient with TSC (76-80). The cases reported are more often females with a median age of 55 years, all with indolent behavior. The immunoprofile (CD117+, CK7 focal) and the electronic microscopy appearance mimics the one of the oncocytoma, however the high-grade morphology, with enlarged nucleoli that resemble viral inclusions, and the cytoplasmic vacuoles are not usually encountered in a classical oncocytoma. FLCN mutation detection can be of help in distinguishing a hybrid tumor from a HOT.

On the other hand, LOT presents diffuse positivity for CK7, invariably CD117-negative and has been described as eosinophilic ChRCC with absence of any consistent chromosomal losses or gains. The cells have a low-grade appearance with often delicate perinuclear clearing. The 28 cases published consisted in single small tumors with indolent course, slightly prevalent in females with a median age of 66 years (81-83) (*Figure 3C* and *3D*).

MiT family translocation RCC (tRCC)

tRCC accounts for 1-4% of RCC in adult and around 50% of pediatric RCC. They are characterised by gene fusions involving TFE3 or TFEB, 2 members of the MiT family of transcription factors. The most common chromosomal translocations are Xp11, involving the oncogenic activation of the TFE3 transcription factor (*Figure 4A*) and, less frequently, 6;11 (p21;q12), involving TFEB. Xp11 translocation RCCs typically have a papillary/nested growth pattern and are composed of clear cells with frequent associated psammomatous calcifications whereas 6;11 translocations RCC have usually nested architecture and are constituted of a biphasic population of larger and smaller epithelioid cells clustered around hyaline basement membrane material. t(6;11) RCCs are usually indolent (84-86). Among this category, Gupta *et al.* identified 25 cases of TFEB-amplified RCC associated with amplifications of VEGFA (which exists in 6p21, same with TFEB) that showed oncocytic and tubulopapillary features with high-grade nuclei, and their clinical courses were aggressive with metastasis and death from RCC in 46% of cases (87). To date, 54 cases of TFEB-amplified tumors have been reported, a small percentage of which harboring both TFEB translocation and amplification. Overall, TFEB amplified tumors shows high nuclear grade, pseudopapillary/nested/tubular structure and an aggressive clinical behaviour. Notably, 50% of the published cases were negative for TFEB expression by immunohistochemistry (88).

Mucinous tubular spindle cell carcinoma (MTSCC)

Already included as in the 2004 WHO under the name mucinous tubular and spindle cell carcinoma, these tumors often exhibits overlapping histologic and immunophenotypic feature with PRCC type 1. While the classic MTSCC harbors multiple chromosomal losses without the trisomy of chr 7 and 17, the overlapping cases show a chromosomal alteration pattern similar to solid variant of PRCC type 1 cases, including gains of chromosomes 7 and 17 (89,90). To distinguish these tumors with overlapping histology has been recently proposed a new cancer-specific and lineage-specific biomarkers VSTM2A specifically overexpressed in MTSCC (91).

MTSCC generally presents at low pathologic stage at the time of excision, and the majority of the MTSCC with classic histology behave in an indolent fashion. However, presence of high nuclear grade and sarcomatoid features have been associated with lethal outcomes (92,93) (*Figure 4B*).

Renal medullary carcinoma and Collecting duct carcinoma

Renal medullary carcinomas (RMCs) and collecting duct

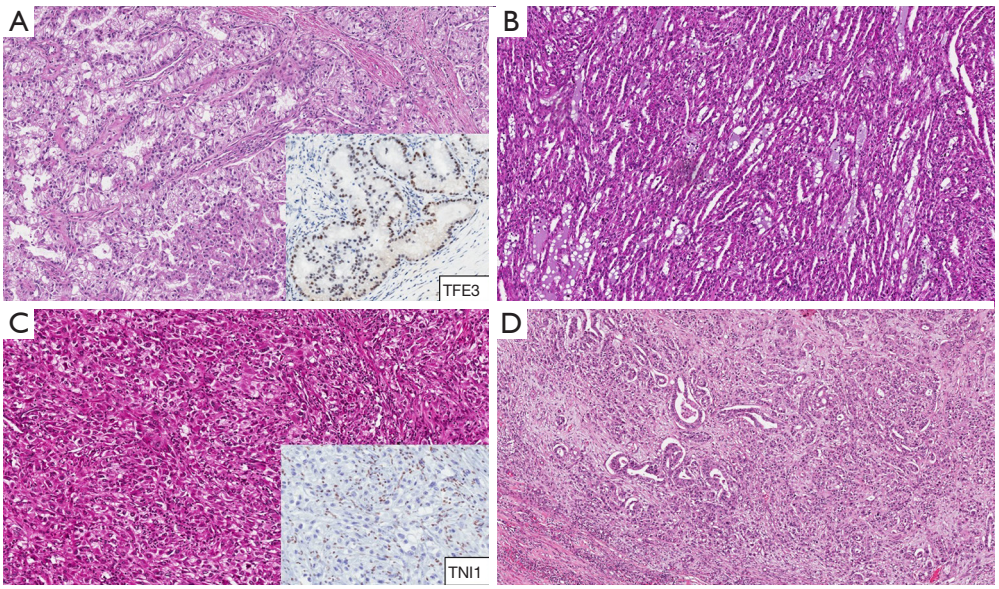

Figure 4 Xp11 translocation RCCs (A, 10×), TFE3 IHC staining (insert); Mucinous tubular spindle cells carcinoma (B, 4×); Renal medullary carcinoma (C, 10×) with loss of SMARCB1 (INI1) expression by IHC (insert); Collecting duct carcinoma (D, 4×).

carcinomas (CDCs) are well-know, rare high grade renal tumors, usually sited in the renal medullary region. They often present at high-stage and are associated with a dismal prognosis. On the basis of the recent modified diagnostic approach and new entities, 25% of tumors previously diagnosed as CDC were reclassified as FH-deficient RCC. Exclusion of metastatic adenocarcinoma, urothelial carcinoma of the pelvi-calyceal system, renal medullary carcinoma, and FH-deficient RCC are required to render a diagnosis of CDC. RMC typically in children or young adults of African, South American and Mediterranean origin with sickle cell trait or disease. The diagnostic criteria for RMC are stricter and include the presence of hemoglobinopathy (sickle cell trait or related hemoglobinopathies and/or finding sickle-shaped erythrocytes (drepanocytes) in the histologic samples) and complete loss of SMARCB1 (INI1) expression by IHC (94-97) (*Figure 4C* and *4D*).

Discussion: recommendations for the next WHO classification

Eosinophilic solid and cystic RCC (ESC RCC)

ESC RCC is an emerging renal tumor entity not yet part of the 2016 WHO classification of genitourinary tumors (4,98,99). It was recently described as a sporadic neoplasms occurring in young women, usually solitary, small and with indolent behavior. Subsequent studies have reported identical tumor also in males and multifocal, in a minority of cases. Metastases have been reported in four cases so far. Ten percent of the patients with tuberous sclerosis-complex (TSC) can present this type of tumor, firstly described with "granular eosinophilic-macrocystic morphology" by Guo *et al.* (100-102). In a case series of unclassified eosinophils tumor in patients of 35 years of age or younger, 30% of the cases were classified as ESC-RCC (17). Solid and cystic architecture, voluminous eosinophilic cytoplasm, granular cytoplasmic stippling, CK20 positivity either diffuse or focal are the typical features of these tumors, although CK 20 negative cases (10-15%) have been reported (*Figure 5A* and *5B*). Next generation sequencing analysis and karyotype profiling evidenced that ESC-RCC are characterized by somatic tuberous sclerosis gene mutations (TSC1 and TSC2) in the great majority of cases and recurring chromosomal copy number gains and losses. Since many of the genes involved in these alterations are part of the regulation of MTOR signaling pathway, therapies targeting the mTOR pathway in these RCC can be considered (103,104).

Biphasic squamoid papillary RCC

Initially reported in 2012 by Petersson *et al.* and later in a

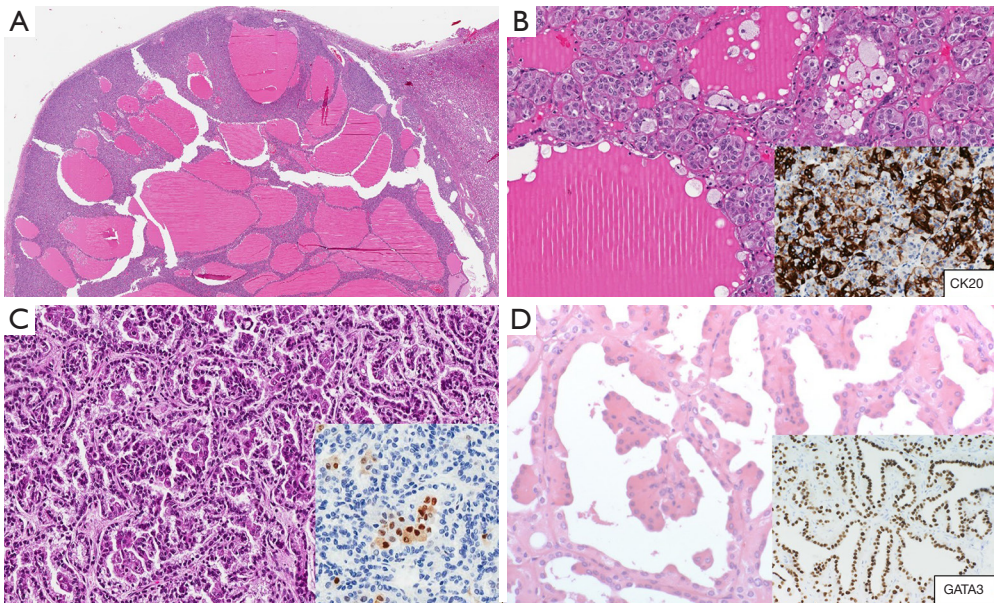

Figure 5 Eosinophilic solid and cystic RCC at low magnification (A, 2×) and high magnification (B, 20×), CK20 expression (insert); Biphasic squamoid papillary RCC (C, 10×), BCL1 IHC stained the squamoid cells (insert); Papillary renal neoplasm with reverse polarity (D, 40×), positive nuclear staining with GATA 3 (insert).

larger series by Hes *et al.* this new entity may represent a distinct subtype of papillary RCC type 1, on the basis of the morphological, immunohistochemical and molecular similarities (105,106).

The name is given by the presence of two cell populations: one constituted by larger eosinophilic cells with abundant cytoplasm and higher-grade nuclei designated as 'squamoid' (squamous cell-like), organized in glomeruloid or micronodular formations resembling alveolar structures; and a population of smaller cells with amphophilic or clear and scant cytoplasm, admixed with the larger cells. These tumors can be multifocal, bilateral, associated with other tumors such as multiple papillary adenomas, papillary RCC, clear cell RCC, and low-grade urothelial carcinoma, and can express malignant behaviour with metastasis, recurrence, or death due to the disease in 15% patients (107-110) (*Figure 5C*).

Papillary renal neoplasm with reverse polarity (PRNRP)

A distinct subset of papillary renal tumors with reverse polarity was recently described by Al-Obaidy and colleagues (111). These tumors are characterized by low-grade nuclear features, inverted nuclear location, eosinophilic cytoplasm, branching papillae with thin fibrovascular cores and indolent clinical behavior. They are characteristically positive for GATA3 and L1CAM and the great majority of them [93% in the series of Kim *et al.* (112)] harbors recurrent mutation of KRAS, whereas no KRAS mutation have been reported in any of papillary type 1 and type 2 cohort used as controls (112,113). After a median follow-up of 54 months, all patients with PRNRP were alive with no evidence of disease (*Figure 5D*) (*Table 1*).

Conclusions

In addition to common histological subtypes known for decades, many entities with distinct morphological and molecular features are under active investigation and may be included in future classifications. The more accurate identification of these tumors with the help of ancillary techniques and genetic analysis will improve patient's stratification and therapy and may have an impact on their families in the specific case of a genetic syndrome-associated RCC.

Table 1 Renal cell tumors and new described entities grouped according to their cellular features/architectural pattern, anatomic location, associated diseases, and genetic alterations

Cellular features and/or Architectural pattern	Anatomic location	Associated diseases	Genetic alterations
• Clear Cell RCC	• Renal medullary carcinomas	• Acquired cystic disease-associated RCC	• TCEB1 RCC
• Papillary RCC	• Collecting duct carcinomas	• RCC in neuroblastoma survivors	• MiT family translocation RCC
• Chromophobe RCC			• FH deficient RCC
• RCC with (angio)leiomyomatous stroma			• ALKRearrangement-associated RCC
• Clear cell papillary RCC			• SDH-deficient neoplasia
• Biphasic squamoid papillary RCC			
• Mucinous tubular spindle cell carcinoma			
• HOT/LOT			
• Eosinophilic solid and cystic RCC			
• Tubulocystic RCC			
• Thyroid like follicular RCC			
• Papillary renal neoplasm with reverse polarity			

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